THE PHENOTYPE OF GLOMERULAR INFILTRATING CELLS DURING ACUTE RENAL ALLOGRAFT REJECTION AND THEIR PREDICTIVE VALUE FOR CLINICAL OUTCOME

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Introduction: In the semi-quantitative Banff classification no clear cut-off value exists to render a diagnosis of glomerulitis and the Banff definition of glomerulitis is based on identification of mononuclear cells and does not include granulocytes. Furthermore, a limited number of studies are available concerning the immunophenotyping of glomerular leukocytes and its relationship to renal allograft outcomes.

Main aim: The aims of this study were phenotype glomerular inflammation during an episode of acute rejection and correlate these components of glomerulitis to antibody-mediated rejection indicators, response to therapy and renal outcome.

Material and Methods:

A) PATIENTS:

• Cohort study with 60 renal transplant patients with biopsy proven acute allograft rejection.

B) METHODS

• All biopsies were reviewed and scored according to the updated Banff '07 classification by a renal pathologist. Only renal biopsies with seven glomeruli or more at least in one of the slides biopsies stained were included.

• Data on C4d were already available from previous studies and routine diagnostic work-up.

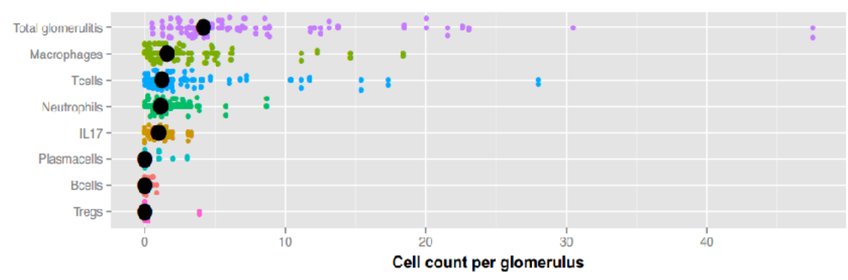
• Immunohistochemically stained cell types were counted as average amount of positive cells per glomerulus. A total glomerulitis cell count was produced by summing CD68, CD3 and CD15+ cells.

• We used two binary outcome measures:

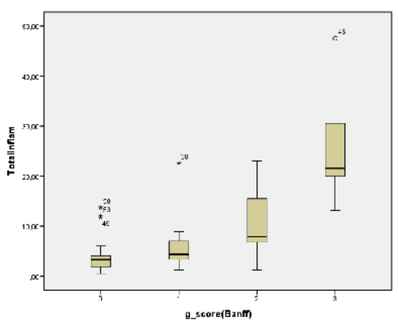
1. Response to therapy was defined as a decrease in serum creatinine level within two weeks after the start of anti-rejection therapy to a maximum of 125% of the value before the diagnosed episode of rejection. The baseline creatinine value was defined as the lowest creatinine value before the rise in creatinine.
2. The second outcome measure was graft failure, defined by the return to long-term dialysis or an eGFR, calculated by the CKD-EPI formula, of <15 ml/min/1.73 m^2 for more than 3 months censored for patient mortality (K/DOQI stage 5).

Results:

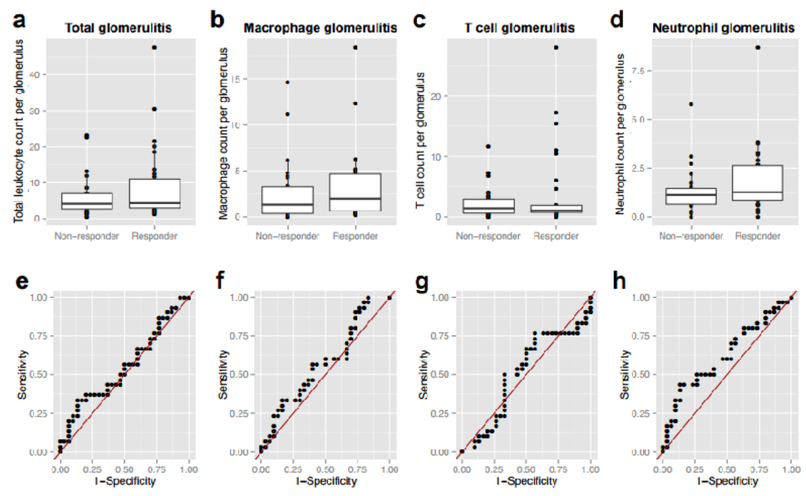
The major contributors to glomerulitis were neutrophils, T cells and macrophages, whereas the other cell types were hardly present. T cells and macrophages were highly correlated (rho 0.66, P < 0.001). Neither glomerular T cells nor macrophages correlated to the neutrophilic glomerulitis (rho -0.03 and 0.22 respectively).



The amount of macrophages and T cells as well as the total glomerulitis cell count (defined as the sum of glomerular neutrophils, T cells and macrophages) increased with an increasing Banff g-score, whereas the amount of neutrophils did not correlate to the Banff g-score. Neither the Banff g-score, nor the T cells, neutrophils or macrophages correlated to C4d positivity.

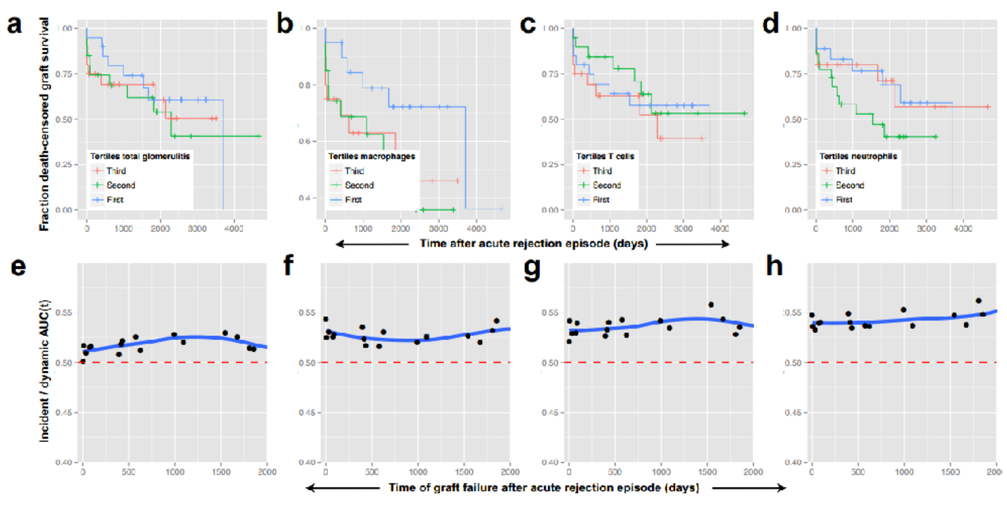


Preliminary results showed that glomerular macrophages correlated to endothelialitis (rho 0.37, P = 0.02). Interestingly, neutrophilic glomerulitis inversely correlated to the extent of transplant glomerulopathy (rho -0.27, P = 0.08) and increase in mesangial matrix (rho -0.32, P = 0.04). None of the cell-types was a bystander effect of the total burden of inflammation (correlation with t-score all P > 0.6). A higher g-score (OR 0.81, [95%CI 0.36-1.79]), total glomerulitis score (OR 1.05, [0.98-1.13]) or any of the three cell-types did not relate to resistance to anti-rejection therapy (OR 1.08 [0.95-1.22], OR 1.06 [0.91-1.23] and OR 1.43 [0.90-2.26] for T cells, macrophages and neutrophils, respectively).



Prediction of clinical response to therapy by glomerular cell counts.

Prediction of death-censored graft failure by glomerular cell counts.



Similar results were seen for the prediction of death-censored graft failure: g-score HR 0.13 [0.66-1.94], total glomerulitis score HR 0.99 [0.94-1.04], T cells HR 0.96 [0.87-1.06], macrophages HR 1.03 [0.93-1.13] and neutrophils HR 0.88 [0.63-1.23]. The accompanying ROC curves rendered low predictive value for the individual patient for both resistance to anti-rejection therapy and death-censored graft failure (AUCmax 0.56).

Conclusion:

Extensive immunophenotypic characterization of glomerulitis during rejection showed 3 main cell types to be present: T cells, macrophages and neutrophils, whereas B cells, mast cells, plasma cells and Tregs were unfrequent. Based on our study, we were unable to show a differential clinical course for the different types of glomerulitis. Our results confirmed a correlation of g-score with the total immflamation score and with specific immunostainings (macrophages and T cells).

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N) Renal Transplantation. N1) Transplantation basic science and immune-tolerance of allogenic and xenogenic transplants.
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DOI: 10.3252/pso.eu.51era.2014

Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM THE NETHERLANDS MAY 31ST JUNE 3RD 2014

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